Thieme

Atherosclerotic Lesions in the Superficial Femoral Artery (SFA) Characterized with Velocity Ratios using Vector Velocity Ultrasound

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ABSTRACT

Purpose Atherosclerotic arteries are challenging to evaluate quantitatively using spectral Doppler ultrasound because of the turbulent flow conditions that occur in relation to the atherosclerotic stenoses. Vector velocity ultrasound is angle independent and provides flow information, which could potentially improve the diagnosis of arterial stenoses. The purpose of the study is to distinguish significant stenoses in the superficial femoral artery (> 50 % diameter reduction) from non-significant stenoses based on velocity ratios derived from the commercially available vector velocity ultrasound technique Vector Flow Imaging (VFI).

Materials and Methods Velocity ratios (intrastenotic blood flow velocity divided by pre- or poststenotic velocity) from a total of 16 atherosclerotic stenoses and plaques in the superficial femoral artery of 11 patients were obtained using VFI. The stenosis degree, expressed as percentage diameter reduction of the artery, was determined from digital subtraction angiography and compared to the velocity ratios.

Results A velocity ratio of 2.5 was found to distinguish clinically relevant stenoses with > 50 % diameter reduction from clinically non-relevant stenoses with < 50 % diameter reduction and the difference was statistically significant.

Conclusion The study indicates that VFI is a potential future tool for the evaluation of arterial stenoses.

Introduction

Atherosclerosis is a systemic disease of the larger arteries causing luminal narrowing leading to cardiovascular diseases, the number one cause of death globally [1]. One subgroup of cardiovascular diseases is peripheral arterial disease (PAD), in particular lower extremity arterial disease.

Digital subtraction angiography (DSA) is the gold standard for vessel analysis. Besides a diagnostic overview of the blood vessels, it allows simultaneous endovascular therapy. However, DSA is invasive, contrast-dependent, and exposes patients and staff to ionizing radiation [2]. Moreover, traditional DSA is a two-dimensional imaging modality, limiting the stenosis assessment to the imaged projection plane. This can lead to inaccurate diameter measurements, especially for elliptic and other complicated vessel shapes.

An alternative to DSA is Doppler ultrasound, which is a diagnostic tool providing information regarding the vessel wall and hemodynamics and is commonly used for evaluation of PAD. Color and spectral Doppler can be used to localize and assess the severity of possible stenoses by estimating the blood flow velocity. The velocity correlates with lumen diameter, but due to interindividual variations of blood flow, velocity ratios, i. e. the intrastenotic velocity divided by the prestenotic velocity, provide better estimates of the stenoses [3, 4]. Velocity ratios are normally calculated on the basis of two individual peak systolic velocity measurements, measured in the stenosis and in a proximal vessel segment with a normal lumen. In previous studies, velocity ratios varying from 1.5 to 2.4 have been shown to distinguish < 50 % stenoses from > 50 % stenoses, where the stenosis degree was based on angiographic diameter reduction [3–7]. The conventional Doppler technique is angle-dependent and operator-reliant, in particular in the presence of stenoses [8, 9]. Operator errors can therefore lead to substantial deviations in velocity estimation and subsequent velocity ratio calculation, and because two individual velocity estimations are needed to provide a ratio, the deviation can be further aggravated.

To circumvent the angle dependency of conventional Doppler, the angle-independent ultrasound technique Vector Flow Imaging (VFI) was proposed by Jensen and Munk [10]. VFI provides simultaneously the axial and transverse velocity components of the blood flow. A conventional ultrasound pulse for flow estimation is transmitted, and the received echoes are beamformed to yield three beams in parallel. One uses conventional beamforming for estimating the axial velocity, and the other two beams are used for estimating the transverse velocity component. By combining the velocity components along the two axes, 2D vector velocities are obtained. VFI using linear arrays has a tissue penetration of 5 cm and is useful on superficial blood vessels. The technique is described further by [10–12], and the clinical use by [13–19].

The aim of the study was to investigate VFI as a technique for the quantitative assessment of PAD. The technique was tested in a small patient group with PAD and clinical indication of stenosis in the superficial femoral artery (SFA). The hypothesis was that velocity ratios derived from VFI can be used to distinguish significant stenoses (> 50 % diameter reduction) from non-significant stenoses. DSA was used as the reference technique to measure vessel diameter.

Materials and Methods

Patients

Thirty consecutive patients scheduled for DSA of the lower extremities due to suspected PAD were examined. Patients were eligible for inclusion if they had one or more previously untreated atherosclerotic lesions (stenosis or plaque) in the SFA. Nineteen patients with previous by-pass surgery, endovascular surgery, occlusion, no lesions (judged by both ultrasound and DSA), or widespread atherosclerotic disease according to the TransAtlantic Inter-Society Consensus Document on Management of PAD (TASC II, [20]) were excluded. 11 of the 30 patients were included, providing a total of 16 lesions consisting of 13 stenoses and 3 plaques.

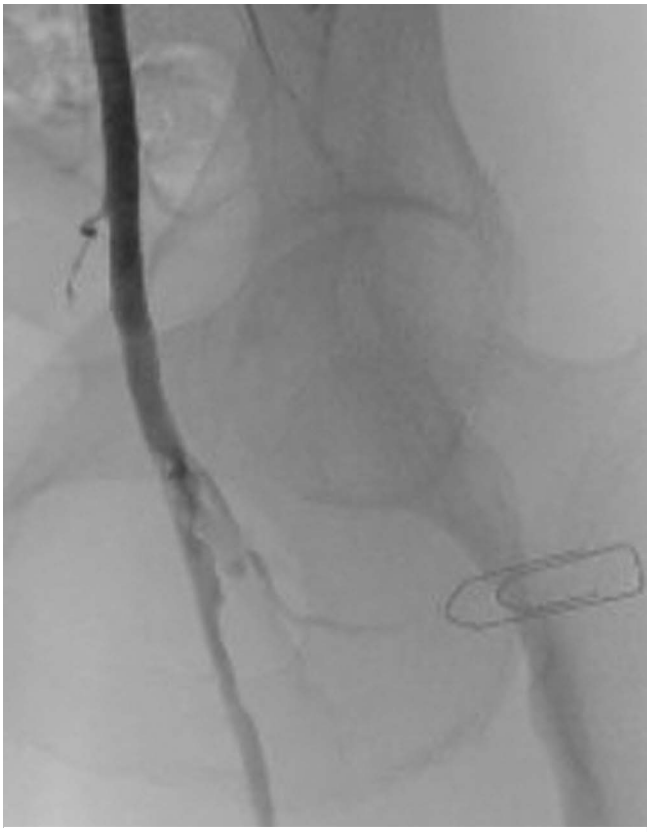
Written informed consent was obtained. The local Ethics Committee waived approval, since ultrasound scanning of atherosclerotic extremities is considered a routine procedure (protocol number: H-4-2013-001).

Scan setup using Vector Flow Imaging

A commercial scanner (UltraView 800, BK Ultrasound, Herlev, Denmark) was used with a linear transducer with a center frequency of 9 MHz (8670, BK Ultrasound, Herlev, Denmark).

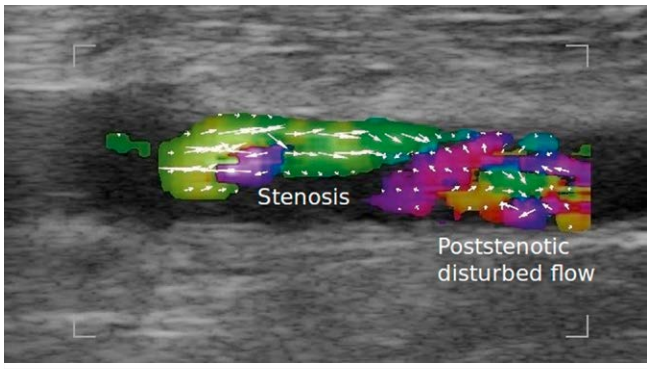
All patients underwent ultrasound scan in the angiography room just prior to DSA, and all were scanned in a supine position after at least 15 min. of rest. The patients' SFAs were scanned longitudinally from the bifurcation of the common femoral artery to the point where the SFA enters the adductor canal. When disturbed flow was detected by VFI, a marker (paper clip) was attached to the patient's thigh corresponding to the location of the flow disturbance ensuring corresponding ultrasound and angiographic recordings (▶ **Fig. 1**). From this location a VFI-sequence of 15 s was recorded with a frame rate of 15 Hz. The recording contained flow both in the lesion and proximal/distal to the lesion. Disturbed flow was defined as the presence of vortices, flow in multiple directions and/or suddenly occurring aliasing indicating increasing flow velocities. VFI provides 2D images of the blood flow, where each pixel contains quantitative information about direction and velocity with superimposed vector arrows to facilitate flow visualization (▶ **Fig. 2**).

The color box is operated similar to color Doppler and was adjusted to cover the vessel and vessel walls. The pulse repetition frequency (PRF) was adjusted to the level providing the best possible

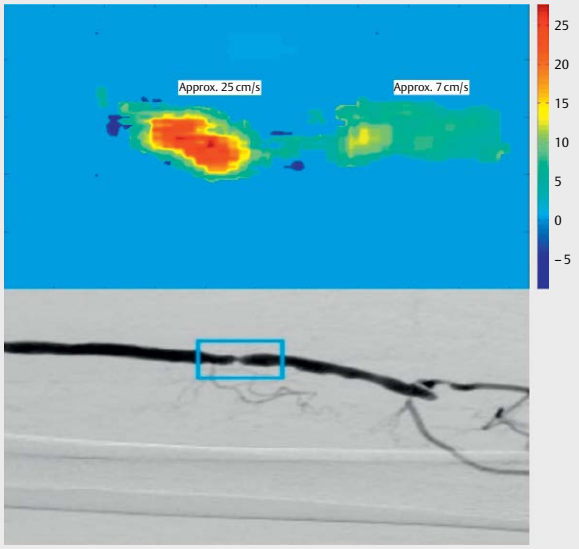


▶ **Fig. 1** DSA with paper clip marker indicating the stenosis (patient 7).

filling of the vessel, even if aliasing still was present in peak systole. If the PRF was adjusted to the level where no aliasing was present, data containing lower flow velocities would be neglected. The angle of insonation was 70-90 degrees in all cases.



▶ **Fig. 2** Scanning of a stenosis (patient 4) using VFI. The arrows illustrate flow direction and relative velocity magnitude. The arrows are for illustrative purposes only and are not used for the quantitative estimation of velocity and direction. The blood flows from left to right as indicated by the arrows in the green area. Aliasing indicating higher flow velocities is seen in the purple area to the left and poststenotic disturbed flow is seen to the right. Notice the angle of insonation of 90°.



▶ **Fig. 3** The top image shows the MATLAB processed VFI recording of the stenosis illustrated by the DSA in the lower image (patient 3). The top image represents the part of the vessel shown in the blue box in the lower image with the clinically relevant stenosis in the middle. The color bar to the right of the top image shows the velocity range in cm/s for this specific frame. The color bar is not used for quantitative estimation, only for orientation. The blood flows from left to right. Maximum velocities around 25 cm/s are detected in the red area and in the turquoise area to the right of the stenosis velocities around 7 cm/s are detected. The yellow area immediately poststenotic represents the flow jet with a velocity of 13-14 cm/s. These velocities are obtained from a random point in the cardiac cycle where the best possible filling of the vessel is seen without aliasing being present. The marker is not visible in this projection.

Previous VFI studies performed on a flow rig and in-vivo indicated a negative bias around -10 % for velocity estimations [12, 13]. This is due to a bias in the estimation scheme, which can be compensated for in an optimized setup as demonstrated by Jensen et al. [21]. However, in this study determination of the exact velocities is not relevant, since the velocity estimations are used to calculate velocity ratios, and thus, any systematic error is removed.

Angiography

An Infinix-i system (model INFX-8000 V, Toshiba Medical Systems Corporation, Tochigi-ken, Japan) was used for DSA. Puncture of the common femoral artery was performed followed by placement of a 5 French sheath. A 4 or 5 French catheter was used for contrast injections and DSA was performed using 2 frames/s and a 6-10 ml. contrast injection (Visipaque 270 mgI/ml). Routine anteroposterior images in one plane were recorded and occasionally supplemented by oblique projections. Subsequent measurements were performed on a standard workstation. From the region of interest (marked with the paper clip), the image yielding the most severe diameter reduction was used for calculation of the stenosis degree percentage. This was calculated using the smallest diameter in the stenosis versus the diameter in an adjacent normal arterial segment. A stenosis degree of 40 % corresponds to a vessel diameter reduced by 40 % compared to the normal vessel. Disturbed flow detected with VFI with no corresponding diameter reduction in any of the DSA images was defined as an atherosclerotic plaque. Stenosis degree percentage was calculated independently of the ultrasound scanning by a radiologist not otherwise involved in the study.

Velocity ratios calculated from VFI

The VFI recordings were analyzed off-line with in-house MATLAB scripts (MathWorks, Natick, MA, USA) with a point-and-click interface providing the velocity and direction for each pixel. From each recording, three frames illustrating flow with the best possible filling of the vessel in both the lesion and healthy part of the SFA were selected. The velocity ratio was then calculated as the maximum velocity detected as centrally as possible in the lesion divided by the maximum velocity detected centrally in the adjacent disease-free segment. In three cases the challenge was to obtain velocities upstream of the stenosis, and thus, only downstream velocities were measured. No measurements were made in the turbulence immediately downstream of the stenosis. Both velocities were obtained from the same frame, and as far from each other as possible within the width of the transducer. Only velocities with a flow direction parallel to the vessel wall were used, excluding velocities in regions of turbulence. The maximum velocities were located manually in each selected frame from the colored pixels of VFI via the point-and-click interface (▶ **Fig. 3**). The final velocity ratio was calculated as the average of the velocity ratios from the three frames. If shadowing from a calcified plaque in the superficial vessel wall was present, maximum velocities were obtained from either side of the shadow, and the velocity obtained distal to the lesion was divided with the velocity obtained proximal to the lesion.

Assuming a high level of arterial stiffness due to atherosclerosis throughout the SFA, the relationship between the cross-sectional

▶ **Table 1** Velocity ratios and corresponding stenosis degrees.

Patient number	Lesion number	Lesion type	Velocity ratios	Average velocity ratio	Degree of stenosis (%)
1	1	Stenosis	2.1, 1.9, 2.7	2.2	78
	2	Plaque	1.1, 0.9, 1.2	1.1	0
2	1	Plaque	0.9, 1, 1	1	0
	2	Stenosis	1.2, 1.2, 1.3	1.2	19
3	1	Stenosis	2.6, 3.6, 2.6	2.9	68
4	1	Stenosis	1.6, 4.4, 1.7	2.6	65
5	1	Stenosis	1.2, 1, 1.3	1.2	37
	2	Stenosis	0.7, 0.8, 1.3	0.9	31
6	1	Stenosis	2.4, 1.8, 2.1	2.1	33
	2	Stenosis	1.3, 1.6, 1.5	1.5	15
	3	Stenosis	1, 1.3, 1.2	1.2	15
7	1	Stenosis	2.1, 2.4, 2.1	2.2	62
8	1	Stenosis	1.9, 2.9, 2.8	2.5	11
9	1	Stenosis	1.2, 1, 1.1	1.1	47
10	1	Plaque	1.3, 1.3, 1.2	1.3	0
11	1	Stenosis	1, 1.1, 1	1	67

Velocity ratios based on VFI recordings from each individual lesion and coherent stenosis degree based on angiographic diameter reduction. A plaque is defined as a flow disturbing lesion with no corresponding angiographic diameter reduction.

areas in the diseased versus the non-diseased vessel segments remains constant during the heart cycle. The relationship between the velocities, i. e. the velocity ratio, remains constant too, when the obtained velocities are from the same point of the cardiac cycle. With a pulse wave velocity of at least 10 m/s [22, 23] and a 4 cm linear transducer the region of the vessel covered by the transducer is passed in maximum 4 ms. With a frame rate of 15 Hz it is therefore assumed that velocities obtained within the same frame are from the same point of the cardiac cycle. All velocity ratios were calculated blinded to the estimation of angiographic stenosis degree.

Statistical analysis

The correlation of average velocity ratios and angiographic stenosis degree was estimated by nonlinear regression analysis. The velocity ratio corresponding to a 50 % stenosis was calculated. Stenoses > 50 % and < 50 % were treated as two different groups, and mean velocity ratios including standard deviations were calculated for each group and compared. An unpaired t-test was performed and $p < 0.05$ was considered significant. All calculations were performed both with and without outliers. To further assess the ability of the velocity ratios to predict stenoses > 50 %, ROC analyses were performed and the AUC was reported. All statistical calculations were performed in LibreOffice Calc except ROC analysis, which was done in R (version 3.3.1).

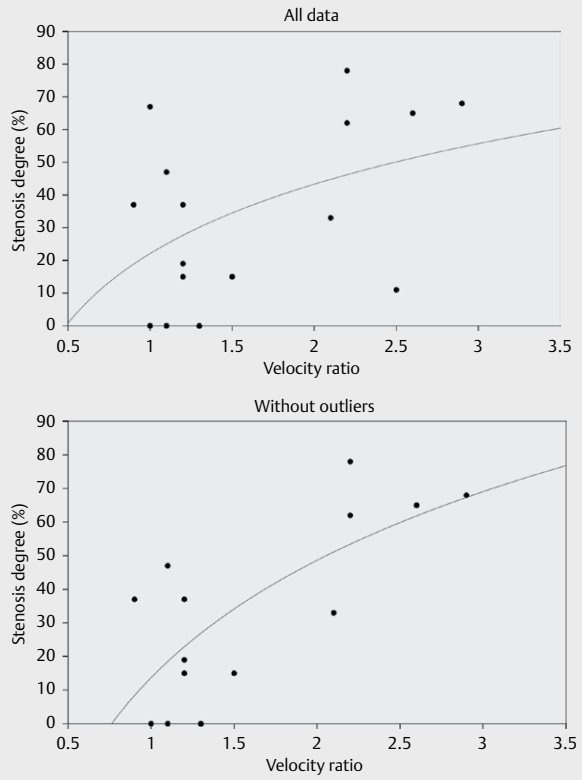
Results

All three calculated velocity ratios, the average velocity ratio, and the angiographic stenosis degree (expressed as percentage reduction) of each lesion are shown in ▶ **Table 1**. Two lesions are considered outliers. Patient 8 has a velocity ratio of 2.5 and a stenosis degree of 11 %, and patient 11 has a velocity ratio of 1 and a stenosis degree of 67 %. The correlation between the average velocity ratios and stenosis degrees is illustrated in ▶ **Fig. 4** with and without the outliers. Without the outliers, the velocity ratio corresponding to a 50 % stenosis is 2.1, and with all lesions included the velocity ratio is 2.5.

With patient 8 and patient 11 excluded from the analysis, the mean velocity ratio (based on the average velocity ratios) for an angiographic stenosis degree < 50 % is 1.3 (standard deviation (SD) 0.34) and the mean velocity ratio for an angiographic stenosis degree > 50 % is 2.5 (SD 0.34). The difference between the two groups is significant ($p < 0.01$). With all patients included in the analysis, the mean velocity ratios for stenosis degrees < 50 % and > 50 % are 1.4 (SD 0.49) and 2.2 (SD 0.72), respectively. The difference is still significant ($p = 0.02$). Based on all patients, the AUC was 0.79 (95 % CI: 0.46 to 1) and excluding the two outliers the AUC was 0.95 (95 % CI: 0.84 to 1).

In patients 3 and 5 (both lesions), the velocity ratios are based on downstream poststenotic velocities, but no significant differences separate them from the remaining ratios based on upstream velocities.

In one case (patient 1, lesion 1) the paper clip marker pointed towards a point approximately 2 cm from the stenosis, and in the remaining cases it pointed directly towards the stenosis.



▶ **Fig. 4** Correlation between average velocity ratios and angiographic diameter reduction expressed as stenosis percentage. The correlation has been illustrated for all data (top) and with the two outliers omitted (bottom). Notice that the ideal correlation line (assuming parabolic flow) starts in (1, 0) with a velocity ratio of 1 when no stenosis is present. The regression lines were generated automatically by LibreOffice Calc.

Discussion

To the authors' knowledge, this study is the first to grade arterial stenoses in the SFA using vector velocity ultrasound. Even though the patient number is small, the obtained velocity ratios of 2.1 (without outliers) and 2.5 (all data) corresponding to a 50 % stenosis match previous larger studies based on spectral Doppler, and the difference between the two patient groups (< 50 % and > 50 % stenosis) is statistically significant, both with and without the outliers. This is further supported by the ROC analysis. The hypothesis of the study is therefore accepted.

Use of VFI is more intuitive than conventional Doppler as angle-independent velocities are provided, thereby making considerations of insonation angle and angle correction unnecessary. Moreover, VFI provides quantitative blood flow information for the full vector map, thus more flow data are available to assess flow changes. This can potentially help physicians diagnose PAD more effectively, spare patients unnecessary examinations, and save time in daily clinical practice. Also, it is not necessary to assume where in the stenotic vessel the peak velocities are found as it is with spectral Doppler when positioning the range gate, as all detected velocities are given within the vector map. However, at this stage the off-line analysis of the VFI recordings described previously is very time-consuming and takes 60–90 min for each lesion. Further development of VFI and implementation of scripts providing all velocities in real-time on the scanner is therefore necessary, before the full potential is exploited and daily clinical use is realistic.

The major limitations of this study are the small patient number and the lack of comparison to conventional spectral Doppler. VFI was not compared to spectral Doppler as the latter is not used in clinical preparations before referral to endovascular interventions at our unit. However, in a future larger scale study, both spectral Doppler measurements and DSA should be regarded as reference standards.

The use of VFI in this study is limited by the manual acquisition of all velocities via the point-and-click interface in the MATLAB scripts. Subsequently, the number of velocity measurements used for each velocity ratio calculation was challenged and vulnerable for erroneous measurements, which may explain outlier patient 11 and the wide range of velocity ratios for patient 4 reported in ▶ **Table 1**. Thus, the process should be automated in future studies.

VFI is dependent on the PRF, and in a stenotic artery with major velocity fluctuations (the velocity increases more than five times when a stenosis exceeds 80 % [3]), numerous frames will be affected by either aliasing, when the PRF is set too low, or no velocity information, when the PRF is set too high. This further limits the number of usable frames from each VFI recording.

To ensure that the velocities measured with VFI are from the same point in the cardiac cycle, the velocities must be obtained within the same frame, limiting the size of the region of interest to the width of the transducer. Another limitation of ultrasonic grading of stenoses, whether VFI or spectral Doppler, is the 2D visualization of the region of interest, which can affect the positioning of the transducer relative to the artery, and hence the velocity estimation [24]. Also, the velocity ratios were calculated by one radiologist only, and inter-observer variation was therefore not found.

The presence of calcified plaques in the vessel wall, and difficult visualization of the small lumen in a severely atherosclerotic vessel provide other ultrasonic challenges. The region of interest can be covered by a shadow, or the maximum velocities are not visualized exactly where expected, e. g. in ▶ **Fig. 3** where peak velocities apparently are detected immediately proximal to the stenosis and not in the stenosis. A possible explanation can be that calcified plaques in the vessel wall disturb the flow signal in the stenotic segment, or the flow can be eccentric in the stenosis and therefore out-of-plane as described for aortic stenosis [25–27]. Another reason could be that the entire stenosis is not visualized sufficiently by DSA because of the given anteroposterior image plane. Hence, the stenosis could actually also cover the vessel segment corresponding to the red area of the ultrasound recording.

DSA is the gold standard for diagnosing and grading PAD, but is, just as ultrasound, a 2D visualization of the vessels, and underestimation of stenoses can therefore occur if the smallest diameter of the vessel is not visible in the angiographic projection. DSA is occasionally supplemented by oblique projections if doubt about a stenosis is raised, but that is no guarantee for a projection illustrating the most severe stenosis. Angiographic underestimation of the stenosis could explain outlier patient 8.

In conclusion, this study has for the first time characterized atherosclerotic stenoses and plaques in the SFA using velocity ratios

obtained with a commercially available vector velocity ultrasound technique. A velocity ratio of 2.5 has been shown to distinguish between stenoses over and under 50 % angiographic diameter reduction, and patients with clinically relevant stenoses > 50 % have been identified with statistical significance. The technique has potential to be used for monitoring atherosclerotic patients and to support the indication of referral to DSA by pointing out and grading potential stenoses in advance, thereby avoiding unnecessary angiographies.

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Conflict of Interest

The authors declare no conflict of interest.

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